REMARKS

With entry of this amendment, claims 1-94 and 96-143 are pending in the application. All of the pending claims are under examination on the merits. Entry of this submission and reconsideration of the application is earnestly solicited.

Status of Application

Applicants note that the Office has entered Applicant's submission and Request for Continued Examination filed August 26, 2002, and has withdrawn the finality of the previous Office Action (Paper No. 22).

Status of File Wrapper

The Office cannot locate the original claims submitted on May 22, 1998, and has therefore requested a replacement copy of the claims. A true copy of the originally filed claims is enclosed herewith.

Claim Objections

Applicants acknowledge that the Office has withdrawn the previous objections to claims 90 and 142 relating to Informalities.

Terminal Disclaimer

Applicants acknowledge that the Office has reviewed, accepted and recorded the Terminal Disclaimer noted by the Office as submitted on July 21, 2003.

Reinstated Rejections Under 35 U.S.C. §§ 102 and 103

The Office previously reconsidered and withdrew rejections of claims 1-4, 6, 7, 10-17, 20, 21, 26, 27, 30, 33-40, 43, 44, 47-49, 52, 54, 56, 57, 59, 61-85, 88-91, 93, 94, 96-116, 118 and 120-143 under 35 U.S.C. 102(e) as allegedly anticipated by, or in the alternative, under 35 U.S.C. 103(a) as allegedly obvious over, Belshe *et al* (5,869,036). Similarly, the Office previously reconsidered and withdrew rejections of claims 18, 19, 28 and 29 under 35 U.S.C. 102(e) as allegedly anticipated by Belshe *et al,* or in the alternative, under 35 U.S.C. 103(a) as allegedly obvious over Belshe *et al* in view of Stokes *et al (Virus Research,* 1993). Similarly,

the Office previously reconsidered and withdrew rejections of claims 51 and 53 under 35 U.S.C. 103(a) as allegedly obvious over Belshe *et al* , and of claims 22-25, 31, 32, 42, 60, 117 and 119 under 35 U.S.C. 103(a) as allegedly obvious over Belshe *et al* in view of Conzelman *(J Gen. Vir.*, 1996).

Each of the foregoing rejections has now been reinstated by the Office, for reasons set forth at pp. 2-6 of the present Office Action.

As an initial point, Applicants note that all of the foregoing rejections were withdrawn following a formal Interview conducted in the case on November 22, 2002, attended by Dr. Brian Murphy, Dr. Peter Collins, Applicants' representative, Jeffrey King, Examiner Brown, and Primary Examiner Park. In addition, a detailed Declaration of Dr. Brian Murphy (executed on August 26, 2002; hereafter, Murphy Declaration) was also submitted presenting extensive evidence that the Belshe et al. reference failed to enable, and therefore failed to anticipate, recovery of any recombinant PIV from cDNA. Applicants' evidence in support of this position was extensive—founded on several, independent grounds as presented in the Murphy Declaration and in Applicants' 8/26/02 Amendment presented in the record (each incorporated herein by reference).

In explaining the withdrawal of these art rejections, the Office reiterated some of the evidence presented in the Murphy Declaration, Interview, and other submissions by Applicants in the record. While the Office's summary did not embrace all of the material facts presented by Applicants regarding non-enablement of Belshe et al., the facts summarized were nonetheless deemed sufficient by the Office to rebut any presumption that the Belshe et al. reference met the requirements of an enabling disclosure for the claimed subject matter. On this basis, the Office made the following determination:

> In view of these deficiencies, one of skill in the art would not have expected to recover recombinant PIV according to Belshe's teachings. (2/21/03 Office Action, Paper No. 32, at p. 4)

In the instant Office Action, the Office has reversed this determination and reinstated the rejections as noted above. To support this reinstatement, the Office submits that Dr. Brian R. Murphy "is an interested party in the present application whose opinion therefore has lower probative value." In addition, the Office argues that:

> 35 U.S.C. 282 and the MPEP 1701 state that '[a] patent shall be presumed valid'. The Office is barred from questioning the validity of a patent claim, and therefore the enablement of a patent claim. The Murphy declaration would have the Office question the validity of the Belshe patent, which the Office is barred from considering.

With regard to the scientific/probative merit of the Murphy Declaration, the Office offers no critical assessment or "weighting" of the facts presented in the Murphy Declaration, nor was any attempt made to identify "opinion" testimony in the Declaration for which the Office might properly assign a "lower probative value." Therefore, Applicants respectfully submit that the evidence provided in Dr. Murphy's Declaration has not been properly received and considered in the present Office Action. A declaration provided by one skilled in the art cannot be dismissed without an adequate explanation of how the declaration fails to rebut the position set forth by the Examiner. In re Alton, 37 U.S.P.Q. 2d 1578, 1582 (Fed. Cir. 1996). Notably, the evidence provided by Dr. Murphy was initially considered sound, and deemed to provide scientific evidence demonstrating that Belshe et al. fails to enable recovery of any recombinant PIV. The Office summarized numerous facts to support this finding in the above-cited Action (Paper No. 32), and there is no apparent, separate "opinion" testimony in the Office's summary that can now be rejected as having been improperly relied upon or assigned undue weight for this initial, favorable conclusion by the Office.

There is in fact no basis in the record to justify any diminution in weight of the facts, opinion, or conclusions rendered by Dr. Murphy. Applicants therefore respectfully request clarification on this point. This should be provided (1) in the form of cited authority showing that Dr. Murphy is in fact an "interested party" (Dr. Murphy has assigned his ownership interests in all of the subject applications to the U.S. Government/National Institutes of Health), and (2) by specifically classifying contested opinion (versus fact) evidence, qualifying the nature and effect of any diminution of weight considered for such contested opinion evidence, and citing factual evidence sufficient to rebut the contested opinion evidence. When, as in the present case, the burden has properly shifted to the Office (i.e., to rebut evidence submitted to show non-enablement of an allegedly anticipatory reference), the Office must respond with evidence that is inconsistent with Applicants' assertions regarding patentability (see, e.g., In re Marzocchi et al., 169 USPQ 367 (CCPA 1971)). This burden requires specific rebuttal of all disputed, material

facts, and remains despite any diminution in weight that may be applied to the evidence put forth by Applicants.

Concerning the Office's statement in the record that "[t]he Office is barred from questioning the validity of a patent claim, and therefore the enablement of a patent claim", this statement is not supported in the present context. As a preliminary point, the Office routinely questions and invalidates patent claims, e.g., in the contexts of interferences, reexaminations, etc. In the present context, the constraint on review suggested by the Office would amount to an egregious breach of public policy. The Office cites 35 U.S.C. 282 and the MPEP 1701 as allegedly requiring that '[a] patent shall be presumed valid'. In fact, the full text of the cited Code section only specifies that the claims of a patent are to be presumed valid. It is not believed that any presumption of validity applies to the specification of a patent, i.e., apart from the claims. Moreover, a key defense to this presumption of validity, is: 35 U.S.C. 282 (3)-- "Invalidity of the patent or any claim in suit for failure to comply with any requirement of sections 112 or 251 of this title" (underscore added).

It is well established that the Office bears a direct burden, whenever it relies upon an anticipatory reference under 35 U.S.C. § 102, to demonstrate that the reference discloses each and every element of the claimed invention. Continental Can Co. USA v. Monsanto Co., 20 USPQ2d 1746 (Fed. Cir. 1991). To meet this requirement, the cited reference must fulfill all of the written description and enablement requirements of 35 U.S.C. § 112 commensurate with the rejected claims. This requirement was explained by the Federal Circuit in In re Donohue, 226 USPQ 619, (Fed. Cir. 1985).

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it.
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> ***
>
> [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. (emphasis supplied, citing In re Borst, 45 USPQ 544, 557 (CCPA 1965), cert. den. 382 U.S. 973, 148, USPQ 771 (1966).

More recently, the Federal Circuit in Elan Pharmaceuticals and Athena Neurosciences v. Mayo Foundation (10/2/03; No. 00-1467) summarized these legal principles as follows:

> To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. 'A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.' Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ('To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.'); PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ('To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.')

The assertion by the Office that it "is barred from questioning the validity of a patent claim, and therefore the enablement of a patent" is clearly contravened by this authority. In fact, the Office bears a duty to establish that a reference relied upon to show anticipation fulfills all statutory requirements so as to fully support the rejected claims. Even if a *prima facie* showing is offered on the basis that patented subject matter is presumptively valid, this does not relieve the Office of its burden of proof. When, as in the present case, cogent scientific evidence is provided to rebut any presumption of enablement, the burden then shifts to the Office to rebut such evidence on scientific grounds sufficient to prove that the reference is in fact enabling for the full scope of subject matter claimed by the applicant.

The Office also justifies reinstatement of the Belshe et al. rejection in the application, and further qualifies its allegedly limited capacity to critically review the Belshe et al. disclosure, as follows:

> [T]he declaration further fails to persuade because the standard for enablement for a reference is that the reference teach how to make the invention, not use the invention. (Office Action Paper No. 38, at p. 4)

This statement is also contravened by the foregoing authority, which expressly requires that an anticipatory reference "also must enable one of skill in the art to make and use the claimed invention.' (Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512, Fed. Cir. 2001).

Turning now to the present Office Action, the Office begins by presenting a summary (albeit incomplete) of facts supported by the Murphy Declaration. Then, the Office Action presents a blanket reinstatement of the Belshe et al. rejections, on very limited facts. The principal foundation for the reinstated rejections relied upon by the Office relates to enablement of "products" versus "methods". In particular, the Office states that:

> Paragraph 10 of the Declaration correctly states that 'the Belshe et al. specification fails to provide a single example of a recombinant PIV recovered from a cDNA' The Office agrees that Belshe did not teach the recovery of PIV from cDNA, however a product is a product, regardless of the means by which it was made." (Paper No. 38, at p. 5, underscore added)

Elsewhere in the Office Action, the Office asserts that:

> In paragraph 7, Declarant states that Belshe did not recover 'an actual recombinant PIV'. However, Belshe did recover a recombinant PIV by another method other than via cDNA, as accomplished by Applicant. Example 6(column 17) of Belshe discloses that cp45 virus replicated in L-gene-transfected CV-1 cells was produced, recovered, examined and found to maintain the temperature sensitive property of the cp45 virus. Applicant's claims are directed to a product, a species of which has been made by other means than cDNA. The process by which the product is made does not render the product novel and unobvious. (id., at p. 4)

These assertions are also contrary to the evidence of record in the instant case, including the previously-submitted Declaration of Dr. Murphy. This evidence clearly evinces that the Belshe et al. disclosure fails to meet enablement standards for any recombinant PIV. By extension, the Belshe et al. reference even more clearly fails to enable recombinant, chimeric PIVs having a genome or antigenome recombinantly modified to incorporate a heterologous PIV sequence to form a "chimeric PIV genome or antigenome", and optionally incorporating one or more temperature sensitive mutation(s) or other attenuating modification(s), for use in immunogenic compositions and methods--as first produced and characterized in Applicants' present disclosure.

The Office directly equates Applicant's claimed, recombinant chimeric PIV products with the alleged "recombinant PIV" recovered by Belshe et al. This is believed to be a

fundamental error, the resolution of which should support prompt allowance of the instantly pending claims. In particular, the Office states that, "[t]he Office agrees that Belshe did not teach the recovery of PIV from cDNA, however, a product is a product, regardless of the means by which it was made." This characterization ignores express structural and functional distinctions in the claimed products over the non-recombinant PIV described by Belshe et al.

These distinctions are clarified by reference to the Declaration of Dr. Murphy, at ¶ 7:

> [T]he Belshe et al. specification only hypothetically discusses the possibility of recovering a recombinant PIV from cDNA. No such cDNA nor recombinant PIV is actually described in structural terms that would qualify as a "written description" of such materials, and it is apparent that no "working example" of a cDNA encoding a recombinant PIV, nor of an actual recombinant PIV, is provided by the Belshe et al. disclosure. Additionally, considering the level of predictability in the art prior to the discoveries presented in the instant application, the teachings of Belshe et al. would not have been considered to provide an "enabling" disclosure of the presently claimed invention. That is to say, Belshe et al. offer such limited direction and guidance that, even when supplemented by available knowledge in the art at the time the instant application was filed, the skilled artisan would not have considered the public to be placed "in possession of" a recombinant PIV produced from cDNA. This conclusion, and the related conclusions below, relate to the fundamental technology of the present invention, i.e., successful recovery of a viable, self-replicating, recombinant PIV from cDNA. It is even more clear that certain detailed aspects of the invention, e.g., involving identification and manipulation of attenuating mutations and their introduction, singly and in combination, into a recombinant PIV, and successful recovery of chimeric PIVs, and attenuated chimeric PIVs, are neither disclosed nor suggested by Belshe et al.

As further clarified by Dr. Murphy in paragraph 8 of his Declaration:

> Concerning more detailed aspects of the invention, the results provided by the instant disclosure allow production of singly and multiply attenuated, recombinant PIVs, chimeric PIVs, and attenuated chimeric PIVs, that are sufficiently infectious in a mammalian host to generate a desired immune response yet are suitably attenuated for selection and development as PIV vaccine candidates. That these novel results were achieved within the instant invention was even more surprising than the basic recovery of recombinant PIV, based on the limited teachings of Belshe et al.

> combined with general knowledge in the art at the time of the invention.
>
> Contrary to the Office's position, the "products" set forth in the instant claims are not distinguished from the non-recombinant PIV of Belshe et al. solely by the process by which the virus is obtained. Instead, as noted by Dr. Murphy, the Belshe et al. disclosure lacks parity with the instant claims for failure to recite a recombinant PIV in "structural terms" that would anticipate or render obvious the instantly claimed products.

The PIV of Belshe et al. is not a chimeric virus. It does not, and cannot (without Applicants' novel cDNA recovery method) feature a genome or antigenome that is recombinantly modified to incorporate a heterologous PIV sequence to form a "chimeric genome or antigenome." It is not even an "infectious chimeric" virus as claimed, because it is produced by a simple *in vitro* complementation assay.

The Office cannot ignore these essential, structural terms of Applicants' claims to equate the instant products to an allegedly "recombinant PIV" deduced from the Belshe et al. disclosure. In contrast to Applicants' contributions, the Office has expressly conceded that Belshe and coworkers were limited in their teachings to a simple *in vitro* complementation assay (described to evaluate temperature sensitivity). As Dr. Murphy noted in his Declaration, this limited study was also attended by fundamental flaws in its design and interpretation. Nonetheless, even if the complementation assay results reported by Belshe et al. were accepted as valid, there is no reasonable scientific basis for extrapolating these findings into the context of a complete, infectious virus. Accordingly, Belshe et al. provide no reasonable expectation of success for producing a recombinant PIV that is viable, attenuated, and immunogenic *in vivo*, to say nothing of having a genome or antigenome that is recombinantly modified to incorporate a heterologous PIV sequence to form a chimeric PIV genome or antigenome--as made possible in part only through true recombinant cDNA recovery methods (Murphy Declaration at ¶¶ 10 and 12-13).

The foregoing structural distinctions clearly obviate the rejections under 35 U.S.C. § 102(e). This is apparent even without considering the many additional deficiencies of Belshe et al. noted in the record. Briefly, these additional deficiencies all stem from the fact that Belshe et al. provide only a rudimentary system--in which a plasmid expressing a wild type L protein in a transfected cell monolayer reportedly increased the level of replication of a biologically derived

PIV mutant strain, PIV3 cp45. This system notably failed to include a control plasmid containing the cp45 mutations, whereby the differences identified in the complementation assay cannot be ascribed to sequence differences between the wild type and cp45 PIV3 L protein--contrary to the assertions of Belshe and coworkers (Murphy Declaration at ¶ 11). In addition, the L cDNA employed by Belshe et al. was never evaluated for its effect on replication of wild type HPIV3. This represents "a critical control", which precludes the possibility that the observed increase in virus replication was simply due to increased expression of L protein (an aberration defined as a "dose effect" rather than true complementation of a ts defect) (Id.) The assay of Belshe et al. (see Table 3) is also unreliable in other crucial aspects. For example, reported positive results in the complementation assay contain internal inconsistencies and lack essential verification of important experimental controls. These inconsistencies would have been apparent to the skilled artisan and "would have detracted significantly from the motivation provided by the cited reference and the expectation of success that the artisan would have to practice the presently claimed invention as allegedly taught by Belshe et al." (Murphy Declaration at ¶ 12).

Yet additional evidence is provided in paragraph 13 of Dr. Murphy's Declaration that only as few as 3 or 4 cells, and certainly no more than 330 cells, in the complementation assay of Belshe et al. successfully produced virus, "whereas the remaining several million failed to produce a single particle." On this basis, Dr. Murphy concludes that:

> [E]ven if the complementation is accepted as authentic, it is of such a low efficiency that its significance is highly doubtful. In any case, there are no means for extrapolating findings from such a complementation assay to infectious virus. Thus, the 20-fold increase in the replication seen in the complementation assay cannot be extrapolated to predict or understand the magnitude of the contribution of the L protein mutations to the ts phenotype of cp45, nor what the biological properties of a hybrid virus carrying only these mutations might be. At best, the findings are simply suggestive that the L gene mutations might contribute to some undefined portion of the temperature sensitivity of the cp45 virus. (underscores added)

Also in paragraph 13 of his Declaration, Dr. Murphy notes that the complementation assay of Belshe "relates only to the ts phenotype of cp45, and does not address the attenuation phenotype *in vitro* or *in vivo*." While a ts phenotype often is associated with attenuation, it is not possible to predict that attenuation will indeed result, nor what its level might be. This is

considered by Dr. Murphy to represent "a critical deficiency" in the Belshe et al. disclosure, since the level of attenuation *in vivo* is an important requirement to developing effective immunogenic compositions and methods.

> Only by actually making an infectious recombinant virus, as provided in multiple working examples in the present disclosure, can one assess the *in vivo* attenuation of the virus to determine its usefulness as a vaccine candidate. Again, each of these deficiencies of Belshe et al. would have been clear to the skilled artisan and would have undermined the motivation and expectation of success for practicing the claimed invention following the teachings of Belshe et al.

Dr. Murphy further states in paragraph 14 of his Declaration that:

> Only with the aid of the present disclosure providing a successful cDNA recovery system can the phenotypic effect of any desired mutation (e.g., an attenuating mutation from PIV3 cp45) be evaluated and demonstrated. For example the instant disclosure demonstrates that a ts mutation identified in L can be segregated from complementary or interactive effects of other cp45 mutations. In this context, it is critical for evaluating the speculative teachings of Belshe et al. that at least a representative set of mutations identified and segregated into a viable recombinant vaccine candidate be verified as attenuating, and that such attenuation be balanced sufficiently to yield a protective immune response in susceptible hosts. The simple studies of Belshe et al. were limited to complementation of replication for a cp45 virus using a wild type L plasmid. These studies were only conducted *in vitro* using tissue culture cells, and were not validated by parallel studies *in vivo*. In this context, it was quite possible that recombinant viruses incorporating one or more of the three "temperature sensitive" (ts) mutations in the cp45 L gene mutations would not be attenuating (att) *in vivo*. In particular, a finding that replication of cp45 may be complemented by wild type L protein in tissue culture cells is not clearly predictive that a virus bearing one or more of these mutations would be attenuated *in vivo*.

Additional discussion is provided in paragraphs 15 and 16 of Dr. Murphy's Declaration pertaining to the requirement for fidelity in determining and describing sequence information for cDNAs and plasmids to allow initial generation of a recombinant virus and validation of a successful recovery system. It is noted that the sequence of the cp45 L gene provided by Belshe

et al. was taken directly from published work by others and were previously considered possible attenuating mutations. Those sequences were subsequently found to contain errors, whereas the present application provides the complete, correct sequence of cp45. This information complements the first successful attempt to generate recombinant, chimeric PIVs that are successfully employed as vectors, which optionally incorporate one or more attenuating mutations in the genes encoding the PIV L, C, and F proteins. The present work also provides the first phenotypic analyses and characterization for these novel recombinant PIV mutants.

Examination of Figure 1 of Belshe et al. fails to reveal a useful mutation in the PIV C protein. The Figure instead reiterates incomplete sequence information and analysis previously reported by Stokes et al. From Belshe et al., one would not know that the F or C mutations present in cp45 were attenuating mutations, and that these mutations are useful in cDNA-derived recombinant, chimeric PIV vector constructs. In contrast, the materials and methods provided in the instant disclosure correctly identifies a full complement of attenuating mutations present in cp45, as well as representative attenuating mutations identified in heterologous viruses (e.g., a mutation designated 456 from the respiratory syncytial virus (RSV) L protein, a mutation designated 170 from the Sendai virus C protein, and a mutation designated 1711 mutation from the L protein of bovine PIV3 (BPIV3)) for incorporation into recombinant chimeric vector PIVs of the invention. As summarized by Dr. Murphy at paragraph 15 of the Declaration:

> In this context, the Belshe et al. disclosure provided little new information on the nature of the genetic determinants of the ts phenotype of cp45--only following previous suggestions that one or more mutations in L might specify some portion of the ts phenotype in cp45. In contrast, by describing successful recovery of recombinant PIV from cDNA, and by further incorporating individual and combinatorial mutations from cp45 (from several genes as well as from extragenic portions of the genome) in recombinant PIVs, the instant disclosure dissects and maps out the specific contributions of the individual lesions in cp45 to the attenuation phenotype. Following introduction of these various, representative mutations, singly and in combination, into recombinant PIVs, the ability to achieve an attenuation phenotype using various manipulations, and to fine tune the attenuation phenotype to achieve useful vaccine strains, was established using widely accepted *in vivo* models for attenuation and immunogenic activity in humans.

As noted above, recovery of a recombinant virus from cDNA was not accomplished by Belshe et al. Nonetheless, the reference speculates even further concerning the prospect of chimeric "hybrid" recombinant vaccine viruses (see, e.g., Example 7). However, Belshe et al. clearly fail to describe or provide specific guidelines for construction of a chimeric PIV cDNA construct. Nor does the reference describe and enable methods for recovering such chimeric constructs, or provide actual data characterizing a chimeric PIV *in vitro* or *in vivo* for identifying candidates useful in immunogenic compositions and methods. As summarized by Dr. Murphy in paragraph 17 of his Declaration:

> Thus, although the principal disclosure of Belshe et al. purports to render construction of chimeric PIV and other "hybrid" viruses possible, the reference neither describes, teaches nor suggests the presently claimed subject matter. On the contrary, no specific guidance is provided to enable any kind of cDNA recovery of PIV, much less recovery of a viable, attenuated and infectious chimeric PIV as provided by the instant disclosure. The speculative teachings of Belshe et al. would not have been accepted by the skilled artisan as providing a clear teaching or practical motivation to achieve the presently claimed invention. This conclusion is underscored by the vast diversity of viral "targets" contemplated by Belshe et al. for constructing "hybrid" viruses . . .. (emphasis supplied).

Additional differences between the present disclosure and the Belshe et al. reference relating to the description of a system to recover infectious replicating viruses from cDNA for selection as vaccine candidates are outlined in Tables 1–3 of Dr. Murphy's Declaration, and are briefly addressed in the subsequent paragraphs. Referring to Table 1 and paragraph 18 of the Declaration, it is noted that Belshe et al. fail to provide an accurate sequence of a wild type PIV virus. This is considered by Dr. Murphy to represent "a critical deficiency for describing and enabling the instantly claimed invention." Relating to this conclusion, PIV lacks a proof-reading polymerase and is known to have a high error rate. During cDNA cloning this high error rate is reflected in a relatively large number of sequence differences among clones, which are heightened by additional errors introduced during RT, PCR, and propagation in bacteria. A single point mutation in the 15.4 kb sequence can be sufficient to preclude recovery, and the identification and correction of potential errors presents "a formidable challenge." The sequences described in the prior art and incorporated by Belshe et al. were later modified to

correct errors, and the ultimate recovery of infectious virus verified that the presently described sequence is "viable". From these facts, Dr. Murphy states as follows:

> Thus, Belshe et al. rely on the previously reported sequence by Stokes et al, and there was no evidence at the time that this sequence, shown in the present disclosure to be inaccurate, could have yielded a viable virus. Even if this untested, incorrect sequence were employed successfully to obtain a recombinant virus, it was nonetheless unpredictable whether the sequence would specify a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*. Thus, Belshe et al. would not have been considered by the skilled artisan to enable recovery of a recombinant PIV3 nor a chimeric vaccine virus, since there was insufficient evidence that the reported sequence would yield these required results. Only the instant disclosure provides an authentic sequence of the full length PIV3 and its contiguous sequences in a plasmid with correct T7 promoter elements, T7 terminators, and hepatitis delta ribozyme. It is noteworthy that during the nearly seven years after the filing date of Belshe et al., Belshe and coworkers have apparently failed to recover any PIV from cDNA. In contrast, the instant disclosure provides a large, fully representative panel of recombinant viruses, including singly and multiply attenuated viruses and chimeric viruses. Among these recombinant viruses, PIV3 and PIV1 viruses and chimeric "vectors" have been constructed and demonstrated to be suitably attenuated and immunogenic to yield protection against PIV1, PIV2, and PIV3. Following these detailed teachings, our lab has progressed into clinical studies for PIV vaccine candidates recovered from cDNAs. (emphasis supplied).

As further clarified by Table 1, and paragraph 20, of the Murphy Declaration, Belshe et al. also fail to describe or enable any specific sequence for an "insert" to yield a chimeric virus that would be compatible for efficient replication. Instead, Belshe et al. simply reference viral proteins, but do not specify any specific sequence of an insert, nor an insert length (see Belshe et al., columns 17– 18). Dr. Murphy concludes that "[s]ince there were many sequence errors existing in the literature, it would not have been possible to determine whether the chimeric viruses prophetically reported by Belshe et al. would be viable, or, if viable, would possess a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*." In contrast, the PIV sequences used in the construction of chimeric cDNAs of the present invention to generate viruses having a chimeric genome or antigenome were obtained from PIVs of known virulence for humans and yielded a chimeric virus with a verified phenotype. Dr.

Murphy summarizes the attendant deficiencies of Belshe et al. as follows:

> The genes that encode the proteins alluded to by Belshe et al. include gene start sequences, a 5' non-coding region, coding region, 3' non-coding region, and gene-end sequence. The exact junctions of the sequences for the inserts referred to by Belshe et al. were not described and therefore one would not have known from the Belshe et al. description whether to include any of the extra-coding sequences or not. For example, the genes from any given virus contain transcription signals that differ from those of another virus, yet it is essential that the "transferred" gene be faithfully expressed in the new, heterologous viral backbone. This critical issue is not even addressed in the Belshe et al. specification. In contrast, the instant disclosure provides exemplary descriptions of an insert, backbone, transcription signals and junctions to yield viable chimeric PIVs that are useful vaccine candidates.

Yet another critical deficiency of Belshe et al. that is considered by Dr. Murphy to be resolved by the present disclosure relates to the length of the viral genome for production of recombinant PIVs (Murphy Declaration at ¶ 21). The length of the PIV genome needs to be an even multiple of six in order to recover authentic copies of virus containing the exact sequence in the cDNA. This "rule of six" reflects the association of each NP monomer with six nucleotides. If the genome does not conform to the rule of six, mutant viruses are recovered that have random mutations that correct the length. According to Dr. Murphy:

> [T]his factor adds a major aspect of uncertainty to the teachings of the Belshe et al. reference, which fails to appreciate the significance of the rule of six and the errors that would arise by failure to properly construct cDNAs in accordance with this requirement." In the instant disclosure, the exact lengths of a full length cDNA for PIV3 (number of nucleotides = 15462) and for PIV3-1 (number of nucleotides = 15516) are provided. This description in turn depended on the actual, successful recovery of recombinant PIVs and subsequent analysis and verification of the fidelity of the viral sequence and phenotype.

As further emphasized by Dr. Murphy, the specific methods used to recover infectious virus also need to be described to enable production of recombinant viruses from cDNAs. Systems to recover negative stranded RNA viruses such as PIV from cDNA are complicated and require a suitable cell capable of both successful transfection by plasmids and replication of the

rescued virus. Dr. Murphy notes that "the recovery of infectious recombinant negative stranded RNA viruses is generally quite inefficient", such that out of 1,000,000 transfected cells, 10 or fewer cells actually produce virus. Particularly for a human pathogen such as PIV3, which does not grow rapidly *in vitro*, it is "a formidable challenge" to successfully produce and recover recombinant virus from cDNA. Considering these factors, Dr. Murphy states that:

> Our studies confirmed that the precise amount of the viral cDNA and support plasmid DNA was critical for initial recovery of recombinant PIV, and this factor was not appreciated by Belshe et al., who failed to even initiate a recovery system. As another example of inadequate guidance, Belshe et al. describe prophetically the use of cDNA expressing a genome sense RNA to recover virus (column 10, line 35). It is now known, however, that for technical reasons the recovery of virus from genome-sense RNA is relatively inefficient at best, and often unsuccessful. An optimal strategy employs a cDNA expressing a positive sense copy of the genome (called an antigenome). This guidance is clearly provided in present disclosure.

In paragraph 23 of his Declaration, Dr. Murphy focuses on the requirement for a complete description of a system to promote expression of viral proteins from support plasmids and from a full-length cDNA to form a functional transcriptase/replicase/genome complex, without which disclosure production of a recombinant PIV from cDNA would not be enabled. Such a "full description" of this system is considered by Dr. Murphy to be lacking in the disclosure of Belshe et al. For example, the system described by Belshe et al. uses a replication competent vaccinia virus expressing T7 (Column 15 of Belshe), but it does not specify how a viable PIV virus would be recoverable in the presence of a vast excess of fully infectious, replication-competent vaccinia virus. Dr. Murphy concludes that "[I]t is unlikely that a low concentration of a recombinant PIV could be biologically separated from the replication-competent vaccinia." This is especially true since vaccinia virus is highly permissive for most cell types and is extremely difficult to fully neutralize with antibody. In contrast, the methods described in the instant disclosure recognize and employ a replication deficient vaccinia virus (MVA-T7). This adaptation permitted the successful recovery of a recombinant PIV in the presence of the MVA-T7.

> Thus, Belshe et al. did not describe a system that would have been considered capable of successfully recovering recombinant PIV

> from cDNA, particularly attenuated (or attenuated, chimeric) viruses having further restrictions on replication. (Murphy Declaration at ¶ 23).

Additional discussion provided in Dr. Murphy's Declaration (at ¶ 24) points to other significant "complexities and uncertainties" for successful recovery of PIV from cDNA that were not overcome by Belshe et al. In particular, Dr. Murphy cites unsuccessful work by others in the field attempting to achieve recovery of other infectious recombinant negative strand RNA viruses. For example, despite extensive foundational research and discovery aimed at recovering a recombinant measles virus, successful production of the recombinant measles virus from cDNA was not reported until 5- to 6-year after Ballart et al. (EMBO J. 9:379, 1990) reported construction of a complete cDNA expressing the genome of measles virus under the control of a T7 promoter and the recovery of recombinant virus by complementation of this synthetic genome with intracellularly-expressed measles virus proteins. Notably, this report, which parallels in certain aspects the speculative disclosure of Belshe et al., proved to be in error and was retracted. The long delay in achieving a successful measles virus recovery system after the general strategy for recovery was mapped out by Ballart and coworkers underscores "the formidable technical and conceptual challenges that must be met to achieve a successful recovery system" for any negative stranded RNA virus (Murphy Declaration at ¶ 24). In fact, at this stage of development in the art, "there was genuine concern that successful recovery of any negative strand virus might not be feasible." Thus, the successful recovery of recombinant rabies rhabdovirus in 1994 (Schnell et al 1994 EMBO J. 13:4195) was a "major milestone" (Id.)

From these studies, however, it was not apparent whether such a recovery approach would be successful with paramyxoviruses, which have substantially greater genome size and complexity, more complex sets of protein products, and poorer growth and stability. In work with a second virus, the highly efficient rhabdovirus vesicular stomatitis virus (VSV), it was shown in 1990 that plasmid-expressed proteins could support a biologically derived nucleocapsid (Pattnaik et al, 1990 J. Virol. 64:2948), but two more years were required to develop the capability to express a defective interfering particle from cDNA (Pattnaik et al, 1992 Cell 69:1011) (Id.) Three more years were required to express complete infectious recombinant virus (Lawson et al 1995 Proc. Natl. Acad. Sci. USA 92:4477; Whelan et al, 1995 Proc. Natl. Acad. Sci. USA 92:8388), which also was viewed as "a major achievement" (Roberts and Rose 1998

Virology 247:1). The work with the rhabdoviruses rabies and VSV involved unexpected requirements, such as the need to express the genome in positive sense form, the need to avoid structures causing early termination by the T7 RNA polymerase, and the need to reduce the background of vaccinia virus. Summarizing these developments, Dr. Murphy states as follows:

> In many instances, recovery depended on methods that could not be applied generally to other viruses, such as removal of the vaccinia virus background by filtration (Schnell et al 1994 EMBO J 13:4195, Lawson et al, ibid), which could not be applied to paramyxoviruses because of their large size and hence necessitated the development of alternative strategies. Studies in other nonsegmented negative stranded viruses illustrate still other unexpected requirements, such as the need to express an additional protein, the M2-1 protein, to achieve successful recovery of human respiratory syncytial virus (Collins et al, 1999, Virology 259:251). This brief survey of the literature embraces only to a subset of studies I know to have been undertaken in large numbers of labs across the globe seeking to recover negative stranded RNA viruses from cDNA. Many of those labs that never came close to successful recovery, thus their efforts have gone unreported. In summary, myriad challenges have persisted in the art to development of a successful recovery system for PIV. These challenges underscore the deficiencies of Belshe et al., who provide only vague, generic concepts without documentary experimentation nor demonstration of a feasible recovery system for PIV. At the same time, the slow-developing state of the art, and the high level of unpredictability in the field, emphasize the unexpected nature of results provided within the instant disclosure. (underscore added)

In the closing paragraphs (¶¶ 25-26) of his Declaration, Dr. Murphy briefly contrasts the instant disclosure with that of Belshe et al. in the context of characterizing the *in vivo* activity of a recombinant PIV recovered from cDNA. In this context, Dr. Murphy emphasizes that "[t]he properties of the virus that make it a successful vaccine candidate must be described in detail in a representative assemblage of recombinant species, as provided by the instant disclosure." He points to three possible consequences that can occur when one attempts to recover a wild type PIV3 or a chimeric recombinant virus from cDNA: (1) a recombinant virus is recovered that replicates to levels characteristic of wild type virus or indicative of attenuation; (2) a recombinant virus is recovered that contains one or more inadvertent and unknown sequence errors that render it defective in any of a number of ways; and (3) virus is not recovered, due

either to one or more lethal sequence errors or some deficiency in the recovery strategy or conditions. In addition, when one introduces mutations into such a cDNA intended to attenuate the virus and thereby to render it useful as a vaccine candidate, at least four outcomes are possible: (1) one can increase the virulence of the virus; (2) one can incompletely attenuate the virus; (3) one can achieve a satisfactory level of attenuation such that a virus can be used as a vaccine; and (4) one can over-attenuate a virus or render it non-viable. In reference to the '793 priority specification, Dr. Murphy states that:

> The examples provided in the instant specification fulfill criterion 3 by providing a representative assemblage of recombinant viruses that are suitably attenuated for development as vaccine agents. In contrast, the disclosure of Belshe et al. fails to achieve any of the foregoing possibilities--by virtue of its failure to describe and enable a cDNA construct encoding a recombinant PIV (see Table 1), for failing to recover infectious virus from cDNA (Table 2), and for the lack of testing and characterization of an infectious, recombinant virus (Table 3).

In view of the foregoing evidence and remarks, Applicants respectfully submit that the disclosure of Belshe et al. does not teach or suggest production in a cDNA-based recovery system of any infectious PIV, and particularly a recombinant PIV comprising a genome or antigenome that is modified to incorporate a heterologous PIV sequence to yield a chimeric HPIV, that is optionally attenuated by incorporation of one or more recombinantly introduced mutation(s)--as disclosed in Applicants' specification. On this basis, Applicants respectfully submit that all of the reinstated rejections of claims over Belshe et al., and over Belshe et al. in view of Stokes et al., have been overcome. Concerning the rejections under 35 U.S.C. § 103, the fundamental grounds stated by the Office in support of the rejections are based on the same, limited teachings of Belshe et al. as a primary reference, which are discussed above. In this regard, the Office contends that it would have been obvious to modify "the chimeric PIV of Belshe" using secondary teachings. However, as noted above, Belshe et al. do not disclose a recombinant PIV that would be a potential subject for modification in accordance with the Office's proposal. On the contrary, as discussed in detail in the preceding section, Belshe et al. neither describes nor enables such a recombinant PIV clone. It is even clearer from the preceding discussion that this primary reference does not teach or suggest methods and compositions that would be useful for generating live, attenuated chimeric PIVs for use in

immunogenic compositions and methods commensurate with Applicants' claimed invention. Instead, the Belshe et al. reference provides, at best, an invitation to experiment toward the production of chimeric PIVs of any kind, particularly those modified to incorporate attenuating mutations, chimeric glycoproteins, cytokines and other modifications as disclosed by Applicants. For these reasons, the Belshe et al. reference is notably deficient as a primary reference that would satisfy the Office's interpretation and support the outstanding rejections under 35 U.S.C. § 103. The secondary teachings set forth by the Office clearly fail to rectify the noted deficiencies of the primary reference. In particular, these secondary teachings do not supplement the teachings of Belshe et al. in a direction or manner that would provide the requisite "reasonable expectation of success" for producing live, attenuated, chimeric PIV viruses, suitably attenuated for use in immunogenic compositions and methods.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 455-5575.

Respectfully submitted,
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